

SUMMARY
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ANTHRAX

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Thank you very much for inviting me to be here with you today. My presentation will cover the following:

- History of anthrax
- Clinical features
- Recognizing and diagnosing anthrax disease, including differential diagnosis
- Treatment
- Prevention/Control

HISTORY

- Koch used anthrax to describe the first microbial etiology in 1876
- Anthrax was the first organism for which a live bacterial vaccine was developed, by Louis Pasteur in 1881. Prior to that time anthrax claimed the lives of many cattle and sheep. This was the first vaccine developed against a bacterial disease.
- Anthrax was an occupational disease of people who handled by products from animals in areas where anthrax was endemic.
- Anthrax has several names, including malignant pustule, malignant edema, Siberian plague, black bane, ragpicker's disease, woolsorter's disease

CLINICAL FEATURES

- Anthrax is a Gram-positive, spore-forming bacillus. It turns a dark staining purple or red color on the Gram stain.
- On a blood agar plate, the colonies have a very pearlescent appearance, a very shiny, white appearance, and if you try to pick them up with an instrument, they have a tacky feel to them.
- Anthrax produces a toxin, which is what causes illness. It is not necessarily the organism that causes illness but the toxin the organism produces.

- Anthrax toxin is produced by three proteins contained within the bacteria: lethal factor, protective antigen, and edema factor.
- These three toxins combine in a binary fashion to produce lethal toxin and edema toxin, the toxins responsible for the clinical signs associated with fatal toxic shock and edema that are seen with anthrax.
- Following is a description of how protective antigen enters the cell:
 - The sub-unit of protective antigen binds itself to the cell wall of macrophages once it invades the body.
 - It enters the cell by combining with small amounts of edema factor or lethal factor.
 - PA and at least one of the other proteins have to be present.
 - When this happens with the hundreds of thousands of macrophages in the body at one time, the body's ability to fight off a foreign invader is overwhelmed, and cell death occurs.
- In cutaneous, gastrointestinal, and inhalation anthrax, the anthrax toxin gets through to the regional lymph nodes where it causes hemorrhagic lymphadenitis.
- The toxin then either goes through hematogenous or lymphatic spread to the brain or causes septicemia, toxemia, or pulmonary edema.

Anthrax in Animals

- In animal herbivores, anthrax is a very rapidly progressing disease. The only other rule-out for finding a dead cow in a pasture would be lightning strike. In other words, the animal can go from standing in the pasture one afternoon to being dead the next morning. Actually, the alternative diagnoses would either be lightning strike or anthrax if this is an herbivore.
- Other species also get forms of anthrax. Dogs and pigs would get a pharyngeal form. They do get quite as ill, and time to death is more prolonged. In general, they seem to be a little bit more resistant than cattle and sheep.
- Often the only visible sign of infection in a dead animal is a little blood from the mucous membranes around the nose or from the gastrointestinal system.
- One of the features of anthrax that makes it a problem, which I'll relate a little bit later in this discussion, is the fact that the spores are very, very long living, and they are very resistant to heat and cold.
- Spores can remain viable in the soil for up to 60 years.
- In the natural transmission of the disease, animals ingest the spores while grazing.
- Humans become infected from animal products
 - Cutaneous: direct contact with hides or carcasses
 - Gastrointestinal: ingestion of infected meat
 - Inhalation: inhalation of aerosolized spores

- Anthrax is not transmissible from person to person, which distinguishes it from some of the other Category A diseases, most notably, smallpox.

Anthrax is a Category A Threat Agent

- Because of resistance of the spores in the environment
- Because it is highly pathogenic to humans
- Because the inhalational form masquerades as an influenza-like illness very early in the stages of the disease. Thus, anthrax can be mistaken easily for something else.
- If it is not recognized quickly and treated promptly, treatment will be largely ineffective.
- It doesn't take very sophisticated laboratory equipment to manufacture the spores.
- There is no way to detect anthrax through odor, taste, or color.
- Events of October to December 2001 taught us two specific things about preparedness:
 - We need to learn what the actual risk associated with a certain dose level is.
 - There were people in the post office who may have been exposed to very high doses and who did get ill., On the other hand, the elderly woman in Connecticut who died, probably as a result of a contaminated letter arriving at her home, likely received a very small infectious dose.
 - We learned that the infectious dose of anthrax is possibly lower than previously thought. A lot more work needs to be done to determine the infectious dose in humans.
 - We need to know more about the remediation of contaminated environments. All we know about cleaning up anthrax spores is based on laboratory cleanup where you can take a contaminated instrument and disinfect it in an autoclave. You can't do that to the Brentwood postal facility, and you can't do that to the Hart Senate Office Building. We need to determine when an environment is clean enough and safe enough for people to return to it. These are issues that will need to be grappled with for years to come.

Anthrax as an Occupational Disease

- Anthrax affected veterinarians, ranchers, and people who work with the byproducts from the animals in the United States.
- In the late '50s and early '60s, there were still New England woolen mills operating to make fabric for the lining of men's suits in which fabrics used were from goat hair. People in these mills were at risk of occupational exposure to anthrax.
- In Africa, there is risk of anthrax from exposure to contaminated meat, and there are periodic outbreaks of gastrointestinal anthrax. It is not a form of the disease we see in this country.
- In 1979, there was allegedly an accidental release of anthrax spores from a facility in Sverdlosk, which caused a fairly high number of illnesses and death.

Worldwide Distribution of Anthrax in its Natural Form

- Disease absent/sporadic in northern Europe
- More common in Greece, Italy, Spain, Turkey, Yugoslavia
- U. S. – endemic in animals in the Dakotas, Nebraska, Oklahoma, Texas
- Enzootic in Central America, Peru, Bolivia, Venezuela
- Hyperendemic in Middle East and adjoining countries of former USSR republics where there is a lack of veterinary expertise to detect the illness
- Largest recent epidemic: Zimbabwe, 1978-80 with 10,000 human cases gastrointestinal anthrax
- Disease has been declining since 1957 when an animal vaccine was introduced and when a formaldehyde treatment for hides from endemic countries was instituted.
- A human vaccine was licensed in 1970.
- Until the BT anthrax cases in 2001, there had not been a human case of inhalation anthrax in the US for 25 years.

DIAGNOSIS

Cutaneous Anthrax

- About 95% of human anthrax cases result from cutaneous exposure.
- From two to four days following exposure, an ulcer appears, which will then develop into an eschar, which is a very prominent sunken, blackened lesion, like a burn or a very bad scar.
- The ulcer is characteristically painless but produces very dramatic edema.
- Anthrax ulcers usually appear on parts of the arm, hands, or face.
- Mortality is up to 20% if untreated.

Diagnosis of Cutaneous Anthrax

- Eschar formation
- Culture of vesicular fluid or exudate (can be diagnostic if patient hasn't been put on antibiotics)
- Blood culture
- Biopsy (with the right testing, can yield a positive even if the patient is on antibiotics)
- Polymerase chain reaction
- Immunofluorescence and immunohistochemistry
- In the outbreaks in 2001, many of the cutaneous cases were diagnosed by skin biopsy and immunohistochemistry here at CDC despite the fact that many of the people had already been put on antibiotics to get treatment underway.

- Even if you get back a negative blood culture, it is very worthwhile to pursue skin biopsy to get a definitive diagnosis when considering cutaneous anthrax.

Differential Diagnosis of Cutaneous Anthrax

Consider the following in differential diagnosis of a blackened eschar lesion on the arm:

- Spider bite
- Rickettsialpox
- Varicella zoster
- Herpes simplex
- Staphylococcal or streptococcal cellulitis
- Ecthyma gangrenosum
- Ulceroglandular tularemia
- Plague
- Cellulitis, eczema, and tularemia are also possible rule-outs

Gastrointestinal Anthrax

- Rare even in the natural exposure setting
- More common outside the United States
- Associated with eating undercooked contaminated beef.
- Possible that terrorists could choose this route of exposure
- Mortality rate up to 50% without treatment

Inhalation Anthrax

- Highest fatality rate of all forms of anthrax disease
- Incubation period can range from two days up to sixty days. In the 1979 Sverdlosk incident, the last person to become ill manifested symptoms at 42 days post-exposure.
- Infection occurs via inhalation of spores
- Spores are engulfed by macrophages and transported to mediastinal and peribronchial lymph nodes.
- Masquerades as an influenza-like illness. One to two days after exposure victims develop a flu-like illness. By day three, they appear to feel better. Then suddenly by day four or five, they go downhill quite quickly with abrupt development of severe respiratory distress and fever.
- Hemorrhagic mediastinitis
- Hematogenous spread
- Meningitis in 50%
- Case fatality rate before 2001 was 90%.

- Because of multi-drug therapy, aggressive support care, and early recognition in many of the inhalational cases, the case fatality rate in 2001 was 45%.

Diagnosis of Inhalational Anthrax

- Chest radiographs - widened mediastinum, pleural effusions
- Blood or cerebrospinal fluid culture and Gram stain
- Polymerase chain reaction (PCR)
- Immunofluorescence and immunohistochemistry (In 2001, immuno-histochemistry of the pleural fluid was diagnostic in situations where people were already put on antibiotics and blood culture was negative. Think of this as a very valuable diagnostic test for anthrax.)
- Autopsy specimens from one of the patients with inhalation anthrax in 2001 showed mediastinal lymphadenitis on x-ray and enlarged, hemorrhagic peri bronchial lymph nodes

Differential Diagnosis of Inhalational Anthrax

- Points to consider in patients who present with sudden onset, with chest x-rays showing pulmonary infiltrates or pleural effusion:
 - Mycoplasmal pneumonia
 - Legionnaires' disease
 - Psittacosis
 - Tularemia
 - Q fever
 - Viral pneumonia
 - Histoplasmosis (fibrous mediastinitis)
 - Coccidioidomycosis

Distinguishing between Anthrax and Influenza-Like Illness

- Not a lot to go on
- People with flu-like illness generally have nasal congestion and runny nose.
- Influenza not usually associated with radiographic findings of pneumonia
- Anthrax not associated with person-to-person spread
- Rapid influenza testing and viral culture useful to indicate whether viruses are circulating among specific populations
- With anthrax, there will be the characteristic abnormal chest x-ray.
- With anthrax, there likely will not be person-to-person spread such as among family members unless there was a common source of exposure to anthrax.

TREATMENT

Assumptions:

These are the assumptions we made for treating inhalation anthrax in the 2001 outbreak given that we had not experienced an outbreak of inhalational anthrax for almost 50 years. This was the first time that modern medicine was employed to treat this disease. We assumed that:

- It would be a systemic illness and that there was possibility of penicillin resistance, and that was borne out by some of the samples taken from patients from several of the sites
- It was toxin mediated
- It would be associated with a high fatality rate

In addition, testing of isolates from Florida, New York, and the District of Columbia showed that beta-lactamase was present.

Treatment Strategy, 2001 Outbreaks

- Employed early, aggressive treatment
- Used combination therapy
- Avoided penicillins, at least until blood culture results were known
- Antitoxin was not available
- Role of steroids was questionable
- Treated for 60 days total in light of prolonged incubation period

Recommended Treatment

- Cutaneous anthrax:
 - Ciprofloxacin 500mg BID PO or Doxycycline 100 mg BID PO
- Inhalation anthrax:
 - Ciprofloxacin 400 mg IV BID or doxycycline 100 mg BID IV
 - May switch to PO when clinically appropriate
 - Appropriate doses
 - 14 days duration
- Ciprofloxacin or doxycycline also recommended as initial therapy for children
- Consider switching to penicillin after antibiotics susceptibility test results become available

Post-Exposure Prophylaxis

- Adults (including pregnant women and immunocompromised)
 - Ciprofloxacin 500 mg PO BID OR
 - Doxycycline 100 mg PO BID

- 60 days duration

Children

- Ciprofloxacin 10-15 mg/kg PO Q 12 hrs OR
- Doxycycline:
 - >8 yrs and >45 kg: 100 mg PO BID
 - >8 yrs and ≤45 kg: 2.2 mg/kg PO BID
 - ≤8 yrs: 2.2 mg/kg PO BID
- 60 days duration

PREVENTING AND CONTROLLING HUMAN ANTHRAX DISEASE

- Supervised slaughter and meat inspection
- Reducing exposure through import restriction, biosafety precautions, education
- Vaccination of high-risk human populations
- Treatment and post-exposure prophylaxis
- Livestock vaccination not widely used except in areas where anthrax is endemic, such as Texas and the Dakotas
- Import restrictions on animal products from countries where anthrax is endemic

Human Vaccination

- Committee on Immunization Practices recommends vaccination for laboratorians and the laboratory response network and people who are occupationally exposed in remediating contaminated environments. Remediation workers are recommended for pre-exposure anthrax vaccination right now. At this point, pre-exposure vaccination is not recommended for any other group, and that includes first responders.
- The National Stockpile includes antibiotics and vaccine for treatment and prevention of anthrax.

Anthrax Vaccine

- U. S. anthrax vaccine was licensed in 1970
- Made from a non-encapsulated, toxigenic strain, but without its capsule, the bacteria have lost some of its virulence.
- Produces an antibody response against protective antigen
- Has a very rigorous pre-exposure vaccination schedule: six doses subcutaneously over an 18-month period with a yearly booster.
- Post-exposure is three doses subcutaneously at zero, two, and four weeks plus 60 days of antibiotics
- Labeling calls for caution in immunosuppressed persons
- Contraindicated for pregnant women

- In the 2001 outbreak, vaccine was used under investigational new drug application using informed consent
- In an emergency situation, medical and public health providers need to weigh risk versus benefits of vaccine versus risk of exposure to a deadly disease. Among persons with high risk of exposure to spores, ethical consideration should be given to offering vaccination even to immune compromised and pregnant women
- In terms of the anthrax vaccine and what we know about its efficacy, one of our Epidemic Intelligence Service Officers at CDC, Phil Brachman, was a young physician who wanted to study anthrax during the 50s and 60s when workers in New England woolen mills who worked with goat hair were at risk of anthrax exposure. So Dr. Brachman did a cohort study among these workers. He vaccinated about 379 of them for anthrax, and there were 870 unvaccinated controls. During the period of his study of these New England woolen mills, there was an anthrax outbreak. The results of his study were as follows:
 - Among the people who had been vaccinated, there were three cases of anthrax. They were all cutaneous. Of those three, two had not completed the series, so these were considered people with break-through in vaccinations because of incomplete vaccination.
 - Among the unvaccinated people, there were 23 cases of anthrax. Five of those were inhalation cases. Although the numbers were small, it was calculated against both forms of the disease that the vaccine had an efficacy rate of 93%.
- There were two animal studies of anthrax vaccine done back in the 50s when a lot of biowarfare research was going on. These two studies evaluated the role of vaccine in combination with antibiotics:
 - In the first study, animals that received vaccine along with antibiotics had much higher survival rates than animals who received antibiotics alone.
 - In the second study, there was not so much of a difference, but apparently animals who received both doxycycline and vaccine had slightly higher survival rates than animals receiving doxycycline alone.

Vaccine Safety

- Anthrax vaccine is the only vaccine in the United States that is given subcutaneously.
- It was licensed at a time when many vaccines, such as tetanus and rabies, were given subcutaneously.
- Since then, the labels have changed for these other vaccines, but anthrax, since it was given to so few people, kind of puttered along with this subcutaneous indication.
- Its safety profile is associated with a higher incidence of local reactions, swelling, and tenderness in the arm in 30-60% of recipients.
- Females tend to have higher rates of local reactions than males.

- Systemic reaction rate for anthrax vaccine is similar to other vaccines, such as flu and hepatitis
- Serious side effect profile is also similar to flu and hepatitis.
- In terms of its safety profile, the biggest concern with anthrax has to do with mild local reactions.

IMPORTANCE OF EARLY RECOGNITION

The take-home message in anthrax is that treatment can be very, very effective if you can get it distributed quickly. That's certainly another issue for the stockpile and for state and local health governments to consider: what is the distribution system for antibiotics and vaccine in the event of an anthrax release.

- In a scenario in which 100,000 people were exposed to anthrax via inhalation:
 - No treatment at all yields 35% death rate
 - Treatment initiated day 1 post exposure yields 15% death rate
 - Treatment begun 5 days post exposure yields 35% death rate

CASE STUDIES

- Please see accompanying slides for two case studies of differential diagnosis for anthrax.
 - Case study one: patient had pneumonic plague
 - Case study two: patient had vaccinia acquired from husband in the military who did not properly cover his arm and transmitted vaccinia to his wife
- Take home messages:
 - Specimen selection is extremely important
 - Don't panic.
 - To become infected with anthrax, you have to be exposed to the spores
 - To cause disease, spores have to enter the skin or be swallowed or inhaled
 - Anthrax disease can be prevented after exposure to spores with early treatment with appropriate antibiotics
 - Anthrax is not spread from person to person

ADDITIONAL RESOURCES

- www.aad.org/BioInfo/Biomessage2
- www.who.int/emc-documents/zoonoses/docs
- www.bt.cdc.gov

QUESTIONS AND ANSWERS

Bob Rehm, AHIP

I'm curious to know if there's a detection kit that could be a preliminary lab analysis of any powder that was suspicious powder that was found in the mail or anything like that, that you're aware of.

Nina Marano

There are a number of rapid-detection field test kits that are used by various agencies. The FBI uses them. They are known for being very sensitive but not very specific, so you get false positives. That's one of the frustrating things. It encompasses the ability to be alert for a lot of different reasons and causes a lot of concern and a bit of panic until the differentials of the final diagnostic can be made at the appropriate level lab. That's the laboratory response network lab within the state or at CDC.

That's the current state-of-the-art for the rapid field testing. However, that being said, there are a number of new assays using the technique of preliminary chain reaction, or PCR, assays that are being developed for field use. They are very sophisticated. They are much more specific, as well as sensitive. These are coming along. I can't tell you how quickly they will be applied for field use, but those are the ones that CDC's bioterrorism and rapid response group are evaluating. They are very pleased with what they're seeing, so I'd say the technology is moving along quickly to develop something for use in the field that will be much more useful, maybe, than some of the test kits that are out there right now.

Paul Dillon

King's Daughter's Hospital

At this time, is there any agent out there that you know of that will decontaminate patients without having to retain the run-off water?

Nina Marano

I'm not sure I can answer that question. I can research it for you and get back to you. I think there are probably people within NIOSH who probably can answer that question better than I can. If you can provide me your contact information, or provide it to Dr. Baden, I would be happy to try to find that answer for you.